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CHANNAVAJALA, LAKSHMI SARADA				
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

09/847,945

Applicant(s)

DESAI ET AL.

Examiner

Lakshmi S. Channavajjala

Art Unit

1611

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 October 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,3-5,7-14,17,31-55 and 57-96 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,3-5,7-14,17,31-55 and 57-96 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-85/86)
Paper No(s)/Mail Date 10-14-09
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Receipt of Amendments and Remarks filed 10/14/09 is acknowledged.

Claims **1, 3-5, 7-14, 17, 31-55, 57-96** are pending in this application.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10-14-09 has been entered.

The following rejections of record have been maintained:

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 3-5, 7-14, 17, 31-33, 38-41, 46-49, 54-55, 57-96 are rejected under 35 U.S.C. 103(a) as being unpatentable over Desai et al (5,439, 686) in view of Kunz et al (5,733,925) in further view of Westesen et al (6,197,349).

Desai et al teach an anticancer (antineoplastic) drug, specifically taxol derivatives such as **paclitaxel**, is suspended in a protein walled shell. See abstract. The shell is not greater than about 10 microns, preferably less than 5 microns, and most preferably less than 1 micron (1000 nanometers). See column 5, lines 30-40. For intravenous administration, the particles may have a diameter size from 0.1-5

microns. See column 9, lines 15-16. Desai teaches the method of delivery for the instant particles allows the administration of substantially water insoluble pharmacologically active agents employing a much smaller volume of liquid and requiring greatly reduced administration time relative to administration volumes and times required by prior art delivery systems (e.g., intravenous infusion of approximately one to two liters of fluid over a 24 hour period are required to deliver a typical human dose of 200-400 mg of taxol). See column 3, line 60 to column 4, line 5.

The particles may be formed using biocompatible polymers, proteins, or polysaccharides. A preferred protein for the shell is albumin. See column 6, lines 40-45 and example 4. Taxol exhibits a unique mode of action on microtubule proteins responsible for the formation of the mitotic spindle. See column 1, lines 20-30. Desai teaches administration of the microparticulates are advantageous in targeting specific sites in the body; allows for the administration of water-insoluble actives; reduces administration time. See column 3, lines 60-67 to column 4, lines 1-5. The particles also are stable and low in toxicity. See examples 5 and 7. Example 8 teaches injecting the particles in a ten-minute period.

Desai does not specify the instant methodology of treating non-cancerous cell proliferation in blood vessels. Further, Desai does not teach an amorphous drug. Kunz et al teach methods for **inhibiting stenosis following vascular trauma or disease, cancer, diseases resulting from hyperactivity or hyperplasia of somatic cells**. Example 7 discloses smooth muscle proliferation in the neointima.

Kunz teaches direct or targeted delivery of therapeutic agents to vascular smooth muscle cells. See column 1, lines 15-35. Inhibiting stenosis following angioplasty is contemplated. See column 3, lines 54-62. The dosage forms are preferably in biodegradable microparticulates or nanoparticulates wherein the particles are formed of a polymer-containing matrix that biodegrades. Kunz et al teach conjugating the drug with a binding protein to target the cells and reduce toxicity. Example 7 notes the toxicity of a free drug versus a conjugated drug. See column 14, lines 25-33. Kunz teaches protein-coated particulates. See column 25, line 20 to column 26, line 40. Therapeutic agents such as **taxol or analogs are preferred therapeutic agents that are designed to target the cell activity without killing the cell**. Taxol is taken into the cell and stabilizes the cell from further dividing. See column 4, lines 40-45 and column 13, lines 24-27. Examples of dosages include .001 to 100 mg/kg per day. See column 28, line 48. For prevention of restenosis following angioplasty or an intervention that contributes to the acute proliferation of smooth muscle cells, a single pre-loading dose is given prior to or at the time of intervention with smaller chronic doses given two or three weeks after intervention. For example, a single dose may be administered about 24 hours prior to intervention, while multiple preloading doses may be administered daily for several days prior to intervention. See column 29, lines 10-15. Delivery of the active agents may be intravenous, intra-arterial (stents), or local delivery. See column 30, lines 56-65 and examples for stent deployment. Kunz teaches single administration protocol. See column 36, lines 50-55. Example 6 teaches infusion using a balloon catheter.

Administration to a carotid, femoral, and coronary artery is taught. See examples.

Example 3 teaches administering the dose in less than three to five minutes. Also note example 5 and 14.

Westesen et al teach nanoparticles containing various poorly water-soluble drugs. See abstract. Westesen teaches the use of an amorphous form of the drug to provide for better solubility and bioavailability of poorly water-soluble drugs than utilizing a crystalline form. See column 5, lines 45-56. Generally amorphous forms of a substance exhibit a higher solubility and a faster dissolution than the crystals forms since they do not require lattice energy.

It would have been obvious for one of ordinary skill in the art at the time the invention was made to utilize Desai's protein coated drug (antineoplastic drug taxol) for the treatment of proliferation of non-cancerous cells in blood vessels (restenosis). One would have been motivated to do so since Kunz teaches inhibiting stenosis following vascular trauma, diseases resulting from hyperactivity or hyperplasia of somatic cells using cytotoxic drugs such as taxol or analogs. Kunz teaches taxol or its analogs are preferred therapeutic agents that are designed to target the cell activity without killing the cell. Taxol is taken into the cell and stabilizes the cell from further dividing to reduce atherosclerosis or restenosis since taxol promotes the formation of usually stable microtubules inhibiting the normal dynamic reorganization of the microtubule network required for mitosis and cell proliferation. Furthermore, Desai et al also recognize taxol's unique mode of action on microtubule proteins responsible for the formation of the mitotic spindle. Therefore, one would have expected success by utilizing Desai's taxol

to treat abnormal proliferation in the blood vessels since Kunz teaches taxol is an effective drug that prevents or reduces cell proliferation in the blood vessels.

Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize an amorphous drug form. One would have been motivated to do so since Westesen teaches the use of an amorphous form for better solubility and bioavailability of poorly water-soluble drugs. Moreover, one would reasonably expect success by applying Westesen's teachings to Desai since both are directed to poorly water-insoluble drugs.

Response to Arguments

Applicant's arguments filed 10/14/09 have been fully considered but they are not persuasive. Applicants submitted that the arguments presented in previous response (1/12/09) are incorporated herewith. Applicants' arguments of 1/12/09 have been addressed in the previous action (Final rejection of 4/14/09) and accordingly are incorporated in this action.

Applicants submit that that the Examiner's reasoning is misplaced and has failed to consider the cited references in their entirety. MPEP §2141.03.VI ("A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention."). Further, the Examiner has failed to consider the claimed invention as a whole when applying the references. MPEP § 2141.02.I ("In determining the differences between the prior art and the claims, the question under 35 U.S.C. 103 is not whether the differences themselves would have

been obvious, but whether the claimed invention as a whole would have been obvious.").

Applicants' arguments are not persuasive because while it is true that the prior art teachings should be considered in its entirety, the rationale to support a conclusion that the claim would have been obvious is that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. KSR, 550 U.S. at ___, 82 USPQ2d at 1395; Sakraida v. AG Pro, Inc., 425 U.S. 273, 282, 189 USPQ 449, 453 (1976). In this regard, the examiner clearly showed the claimed elements in the cited prior art and provided the requisite motivation for one of an ordinary skill in the art to combine the references to arrive at the instant claimed invention.

Applicants state that the claims are based on the surprising finding that a nanoparticle composition comprising a drug in amorphous form, coated with a coating consisting essentially of protein, "when administered systemically, can markedly reduce the level of restenosis following balloon angioplasty and stenting," and "can markedly reduce the level of intimal hyperplasia or neointima formation following systemic administration." Page 8, lines 1-7 of the specification. The specification stated that transient exposure (such as that achieved by systemic administration, specifically, infusion over a period of 5 minutes) of a drug, namely, paclitaxel, in the form of nanoparticles coated with a coating consisting essentially of protein, "may alter the

microtubular function of the smooth muscle cells for sustained periods, impairing their mobility and proliferation." Page 25, lines 18-20 of the specification; Examples 7 and 18. Prior to the present invention, it was unpredictable to a person of ordinary skill in the art whether the method of the present invention would be effective in treating hyperplasia of non-cancerous cells in a blood vessel.

Instant rejection have provided references that teach taxol derivatives coated with proteins (Desai) and the use of paclitaxel for treating non-cancerous hyperplasia (Kunz) and further employing amorphous drugs for better dissolution and bioavailability (Westesen). Desai, similar to the instant invention, also recognizes the effects of taxol on microtubular function of the smooth muscle cells. While the instant method is neither anticipated nor rendered obvious by Desai alone, the claimed invention is obvious in light of the combined teachings of Desai, Kunz and Westesen. In response to applicant's argument, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the motivation to employ the composition for treating non-cancerous hyperplasia comes from the teachings of Kunz, who suggest treating stenosis following vascular trauma or diseases resulting from hyperplasia of somatic cells such as smooth muscle cells with

cancer treating compounds such as taxol or its derivatives; and Westesen teaches amorphous form of the drug (poorly soluble drug) for better solubility and availability.

Applicants argue that according to Kunz, an effective treatment of hyperplasia of non-cancerous cells in a blood vessel would entail adequate concentration of the drug at the target site. See Kunz at column 2, lines 37-46. One would not expect that transient exposure (i.e., systemic administration in 30 minutes or less) of an amorphous drug in nanoparticle form, coating with a coating consisting essentially of protein, would provide high enough local concentration of the drug at the desired target site to achieve beneficial effects for the treatment of hyperplasia of non-cancerous cells.

Applicants' argument is not persuasive because the modification of teachings of Desai with the teachings of Kunz and Westesen, and not Kunz alone, results in the instant claimed transient exposure (i.e., systemic administration in 30 minutes or less). This is because Kunz does not teach instant protein coated composition and instead has been cited for the claimed method. Applicants themselves admit that Kunz teaches the claimed method of use because on page 12 of their response, it is stated that Kunz teaches that the therapeutic drug be present over several weeks (continuously) to provide the beneficial effect.

Applicants argue that the reduced administration time in the teachings of Desai is to obviate the need for toxic solvents, such that small volumes may be administered, but fails to treat hyperplasia of non-cancerous cells in a blood vessel and lacks amorphous drug form. It is argued that even though the composition of Desai can be administered at a reduced time relative to those required in the prior art without incurring toxicity,

Desai by no means suggests that such administration regime would provide high enough local drug concentration for a sustained period of time and allow effective treatment of hyperplasia of non-cancerous cells in the blood vessel. Applicants' arguments are not persuasive because if a prima facie case of obviousness is established, the burden shifts to the applicant to come forward with arguments and/or evidence to rebut the prima facie case. See, e.g., *In re Dillon*, 919 F.2d 688, 692, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990). In the instant case, applicants did not provide any evidence that the composition of Desai does not result in the high enough local drug concentration for a sustained period of time and allow effective treatment of hyperplasia of non-cancerous cells in the blood vessel, when combined with Kunz and Westesen.

1. Applicants argue that Kunz discloses a targeted approach where the therapeutic agent is conjugated to a vascular smooth muscle cell binding protein or peptide, which allows the therapeutic agent, be specifically targeted to vascular smooth muscle cells thus increasing the local concentration of the drug. It is argued that Kunz also discloses "sustained release dosage forms," i.e., "a dosage form designed to release a therapeutic agent therefrom for a time period ranging from about 3 to about 21 days," or longer. Kunz is completely silent about systemically administering a composition comprising an amorphous drug in nanoparticle form, coated with a coating consisting essentially of protein in 30 minutes or less for treating hyperplasia of non-cancerous cells in a blood vessel. In response to applicant's argument, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the

structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). As explained before, Kunz is only taught for the use of taxol for the claimed treatment and not for conjugating taxol with VSM cell binding peptide or protein.

Applicant argues that Kunz teaches a targeted approach and also sustained release dosage form i.e., designed to release a therapeutic agent for a time period ranging from about 3 days to 21 days. It is argued that Kunz is completely silent about systematically administering a composition comprising an amorphous drug in a nanoparticle form, coated with a coating consisting essentially of protein in 30 minutes or less, which is unique for the instant invention. Applicant argues that Kunz teaches away from the instant invention since Kunz teaches the drug conjugated to a protein is effective and not the free drug and directs examiner's attention to example 7 of Kunz. Thus, applicant argues that one would have expected that a drug that was not conjugated to a protein would be ineffective. Applicant argues there is not motivated to use the administration method Kunz in Desai's teachings.

The examiner points out that Kunz does not state that the free drugs are not effective. Kunz states that the free drugs have a higher toxicity and the conjugated drugs are more effective. This statement does not mean that the free drug is not effective at all. It should be noted that "A known or obvious composition does not

become patentable simply because it has been described as somewhat inferior to some other product for the same use." In re Gurley, 27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994). Nonetheless, it should be noted that Desai also recognizes the toxicity of the free drug and therefore utilizes a protein to reduce this toxicity. Therefore, Desai does not teach administration of a free drug. Regarding applicant's argument that a skilled artisan would have expected only conjugated drugs to work, it should be noted that Kunz is not limited to only conjugated drugs. Applicant's attention is directed to column 15, lines 40-45. Kunz's the drug may be in biodegradable particles and Desai teaches biodegradable particles. The fact that Kunz's preferred embodiment is directed to conjugated drugs is not a teaching away from the broader disclosure. "Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments." In re Susi, 440 F.2d 442, 169 USPQ 423 (CCPA 1971).

Applicants argue that contrary to Kunz, the present invention is directed to a systemic administration of a therapeutic agent such as paclitaxel, in a nanoparticle form coated with a coating consisting essentially of protein in 30 minutes or less, which produces beneficial effects (exhibit 1 a meeting abstract entitled "Systemic Nanoparticle Albumin-Bound Paclitaxel (nab-Paclitaxel) for the Prevention of In-Stent Restenosis (SNAPIST-II): A Randomized Comparison of Single Dose and Single Dose Plus Repeat Dose at 2 Months."). Applicants argue that a single dose of a composition comprising nanoparticles of paclitaxel coated with albumin (Nab- paclitaxel) administered intravenously was effective in inhibiting restenosis. While the above article has been

considered, the results provided therein do not compare the conjugated and non-conjugated paclitaxel. Furthermore, the motivation to employ paclitaxel of Desai to treat hyperplasia comes from the teachings of Kunz and a skilled artisan would have expected to the argued efficacy with the composition of Desai comprising amorphous particles (Westesen), when employed to treat hyperplasia.

Applicants argue that the Examiner points to Example 8 of Desai as allegedly teaching "the antineoplastic drugs such as taxol in protein shells and it is administered in less than 30 minutes." Pages 7-8 of the Office Action; Applicants state that Example 8 discloses "In vivo Bioavailability of Soybean oil Released from Polymeric Shells," not administration of drug for hyperplasia. However, the citation examiner provided was taken out of context by the applicants. The examiner referred to Example 8 of Desai for the teaching of injecting the particles in a ten-minute period i.e., for the claimed method administration.

Applicant argues that Westesen does not teach a method of treating non-cancerous cell proliferation in blood vessels, or systemically administering an effective amount of a nanoparticle drug composition in less than about 30 minutes for such purpose; and does cure the deficiencies of Kunz and Desai.

As discussed above, Desai is only deficient in the instant method of treating non-cancerous hyperplasia which is cured by the teachings of Kunz's and has been discussed above. Further, Desai is deficient in the teaching of an amorphous form. Thus, Westesen is only relied upon to cure this deficiency. For the reasons stated in the

rejection, Westesen teaches the advantages of using an amorphous form for poorly soluble drugs.

Thus, it is the examiner's position that Desai in view of Kunz and Westesen render the instant invention *prima facie* obvious.

Claims 1, 3-5, 7-14, 17, 31-36, 38-43, 46-51, 54-55, 57-96 are rejected under 35 U.S.C. 103(a) as being unpatentable over Desai et al (5,439, 686) in view of Hunter et al (5,716,981) in further view of Westesen et al (6,197,349).

Desai et al teach an anticancer (anti-neoplastic) drug, specifically taxol derivatives such as **paclitaxel**, is suspended in a protein walled shell. See abstract. The shell is not greater than about 10 microns, preferably less than 5 microns, and most preferably less than 1 micron (1000 nanometers). See column 5, lines 30-40. For intravenous administration, the particles may have a diameter size from 0.1-5 microns. See column 9, lines 15-16. Desai teaches the method of delivery for the instant particles allows the administration of substantially water insoluble pharmacologically active agents employing a much smaller volume of liquid and requiring greatly reduced administration time relative to administration volumes and times required by prior art delivery systems (e.g., intravenous infusion of approximately one to two liters of fluid over a 24 hour period are required to deliver a typical human dose of 200-400 mg of taxol). See column 3, line 60 to column 4, line 5.

The particles may be formed using biocompatible polymers, proteins, or polysaccharides. A preferred protein for the shell is albumin. See column 6, lines 40-45 and example 4. Taxol exhibits a unique mode of action on microtubule proteins responsible for the formation of the mitotic spindle. See column 1, lines 20-30. Desai teaches administration of the microparticulates are advantageous in targeting specific sites in the body; allows for the administration of water-insoluble actives; reduces administration time. See column 3, lines 60-67 to column 4, lines 1-5. The particles also are stable and low in toxicity. See examples 5 and 7. Example 8 teaches injecting the particles in a ten-minute period.

Desai does not teach the instant methodology of treating non-cancerous cell proliferation in blood vessels. Further, Desai does not teach an amorphous drug.

Hunter et al teach anti-angiogenic compositions comprising an anti-angiogenic factor and a polymeric carrier and methods of its use. See abstract and column 3, lines 40-45. Preferably the active compound is a compound that disrupts microtubule function such as **paclitaxel**, **epothilone**, and etc. see column 3, lines 60-65. The polymeric carrier may be chosen from a carbohydrate, protein, or polypeptide such as **albumin**, collagen, and gelatin. See column 18, lines 15-30. Hunter teaches using the composition to coat a stent which is inserted into the body. Delivery may be done through via expandable catheters. See column 4, lines 24-30 and column 22. Hunter teaches the use of the composition to **treat non-tumorigenic angiogenesis dependent diseases**. See column 5, lines 44-46 and column 36, lines 9-15. Specifically Hunter teaches methods of eliminating vascular obstructions in arteries

and veins to prevent recurrent stenosis (**restenosis**) at the site of failed angioplasty and to treat post surgical narrowing. Suitable sites of the stent include iliac, renal, and femoral, and coronary arteries. See column 25, lines 48-67. Hunter teaches treating neointimal hyperplasia wherein a stent is coated with the composition and inserted onto the arteries. See column 36, lines 1-20. The composition may be further administered intrarticularly, intravenously, etc. see column 37, line 67 to column 38, lines 1-10. The microspheres range from 50-nm to 500 microns depending on the particular use. See column 17, lines 25-40. Anti-angiogenic factors may be linked by occlusion in the matrices of the polymer, bound by covalent linkages, or encapsulated in microcapsules. See column 17, lines 1-5. Hunter teaches administering the anti-angiogenic composition using a stent. Example 7 teaches inserting the stent into a rat. It should be noted that insertion of the stent would meet the instant delivery time since the composition is delivered to the site in less than 30 minutes (the time it takes to insert a stent is less than 30 minutes).

Westesen et al teach nanoparticles containing various poorly water-soluble drugs. See abstract. Westesen teaches the use of an amorphous form of the drug to provide for better solubility and bioavailability of poorly water-soluble drugs than utilizing a crystalline form. See column 5, lines 45-56. Generally amorphous forms of a substance exhibit a higher solubility and a faster dissolution than the crystals forms since they do not require lattice energy.

It would have been obvious for one of ordinary skill in the art at the time the invention was made to utilize Desai's protein coated drug (anti-neoplastic drug taxol) for

the treatment of proliferation of non-cancerous cells in blood vessels (restenosis). One would have been motivated to do so since Hunter teaches treating non-tumorigenic angiogenesis dependent diseases including inhibiting stenosis following vascular trauma and neointimal hyperplasia using cytotoxic drugs such as taxol or analogs and epothilone. A skilled artisan would have reasonably expected success since Hunter teaches these therapeutic agents that disrupt microtubule function and thus treat such diseases and Desai et al also recognize taxol's unique mode of action on microtubule proteins responsible for the formation of the mitotic spindle. Therefore, it would have been prima facie obvious to utilize Desai's taxol to treat abnormal proliferation in the blood vessels since Hunter teaches taxol is an effective drug that prevents or reduces cell proliferation in the blood vessels.

Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize an amorphous drug form. One would have been motivated to do so since Westesen teaches the use of an amorphous form for better solubility and bioavailability of poorly water-soluble drugs. Moreover, one would reasonably expect success by applying Westesen's teachings to Desai since both are directed to poorly water-insoluble drugs.

Response to Arguments

Applicant's arguments filed 10/14/09 have been fully considered but they are not persuasive. Applicant arguments regarding Desai and Westesen have been addressed above. Applicants argue that Hunter does not cure the deficiencies of Desai and Westesen because Hunter does not teach or suggest that systemically administering a

therapeutic agent in nanoparticle form, coated in a coating consisting essentially of protein, in 30 minutes or less, would be effective in treating hyperplasia of non-cancerous cells in a blood vessel. The argument is not persuasive because Hunter is taught for the use of paclitaxel in treating hyperplasia and the teaching of a nanoparticle of protein shell comprising the drug comes from Desai.

Applicant argues that Hunter teaches a stent and the instant recitation, "wherein the effective amount of the composition is systemically administered in less than 30 minutes," clearly does not encompass deployment of a stent. It is argued that the delivery by stent is distinct from systemic delivery, as emphasized in the instant application. The arguments are not persuasive because Hunter is not limited to using stents. Hunter teaches administration intrarticularly, intraocularly, intranasally, intradermal, sublingually, orally, topically, intravesically, intrathecally, topically, intravenously, intraperitoneally, intracranially, intramuscularly, and subcutaneously to the disease site. See column 38, lines 1-10. Applicants' arguments that Hunter generally teaches the above routes is not persuasive because Hunter describes the various routes of administration and choosing an appropriate route so as to achieve the desired release of a drug would have been within the scope of a skilled artisan.

Claims 36-37, 44-45, 52-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Desai et al (5,439, 686) in view of Kunz et al (5,733,925) or Hunter respectively in view of Westesen et al (6,197,349) in further view of Gregory (Transplantation, vol. 59, pp. 655-661, 1995).

The teachings of Desai, Kunz, Hunter, and Westesen have been discussed above. Desai teaches the use of immunosuppressants. See column 5, lines 60-63.

The references do not teach the specific use of rapamycin.

Gregory teaches rapamycin is an immunosuppressant, which has an antiproliferative action that is useful in the treatment of arterial thickening after injury such as angioplasty. See page 655.

It would have been obvious for one of ordinary skill in the art at the time the invention was made to combine the teaching of the above references and further use rapamycin to treat restenosis. One would have been motivated to do so with a reasonable expectation of success since Gregory teaches rapamycin is an immunosuppressant, which has an antiproliferative effect and thus is useful in treating restenosis. Therefore, a skilled artisan would have been motivated to further utilize rapamycin for its additive effect in treating restenosis.

Response to Arguments

Applicant's arguments filed 10/14/09 have been considered but not found persuasive. Applicants argue that Gregory teaches rapamycin but fails to cure the deficiencies of the above references. However, the arguments regarding Hunter, Desai, Kunz and Westesen have been addressed above. Since applicants did not argue the teachings of Gregory, the rejection has been maintained.

Claims 1, 3-5, 7-14, 17, 31-33, 34-35, 38-41, 42-43, 46-49, 50-51, 54-55, 57-96 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hunter et al

(5,716,981) by itself or in view of Yapel (4,147,767) in further view of Kunz et al (5,733,925) and Westesen et al (6,197,349).

Hunter et al teach anti-angiogenic compositions comprising an anti-angiogenic factor and a polymeric carrier and methods of its use. See abstract and column 3, lines 40-45. Preferably the active compound is a compound that disrupts microtubule function such as paclitaxel, epothilone, and etc. see column 3, lines 60-65. The polymeric carrier may be chosen from a carbohydrate, protein, or polypeptide such as albumin, collagen, and gelatin. See column 18, lines 15-30. Hunter teaches using the composition to coat a stent which is inserted into the body. Delivery may be done through via expandable catheters. See column 4, lines 24-30 and column 22. Hunter teaches the use of the composition to treat non-tumorigenic angiogenesis dependent diseases. See column 5, lines 44-46 and column 36, lines 9-15. Specifically Hunter teaches methods of eliminating vascular obstructions in arteries and veins to prevent recurrent stenosis at the site of failed angioplasty and to treat post surgical narrowing. Suitable sites of the stent include iliac, renal, and femoral, and coronary arteries. See column 25, lines 48-67. Hunter teaches treating neointimal hyperplasia wherein a stent is coated with the composition and inserted onto the arteries. See column 36, lines 1-20. The composition may be further administered intarticularly, intravenously, etc. see column 37, line 67 to column 38, lines 1-10. The microspheres range from 50-nm to 500 microns depending on the particular use. See column 17, lines 25-40. Anti-angiogenic factors may be linked by occlusion in the matrices of the polymer, bound by covalent linkages, or encapsulated in

microcapsules. See column 17, lines 1-5. Hunter teaches administering the anti-angiogenic composition using a stent. Example 7 teaches inserting the stent is into a rat. It should be noted that insertion of the stent would meet the instant delivery time since the composition is delivered to the site in less than 30 minutes (the time it takes to insert a stent is less than 30 minutes).

The use of albumin as the polymeric carrier is not immediately envisaged and the examiner relies on Yapel to specifically provide motivation to use albumin. Further, although it appears that Hunter implicitly teaches the delivery time, Hunter does not specify the instant administration time and the examiner relies on Kunz for this teaching. Lastly, Hunter does not specify the drug form and the examiner relies on Westesen to teach this.

Yapel teaches albumin (HAS) medicament carrier suited for intravascular injections. Yapel teaches compared to prior art polymeric carriers has advantages such as ability to administer insoluble drugs; localizes the drug in the capillaries and the drug is released at the intended site and reduces toxic side effects which is especially useful for anti-neoplastic drugs; the absence of emboli formation wherein albumin carriers are administered; ease of preparation; nonantigenicity; capability of carrying a variety of drugs. See column 2, line 50 to column 3, lines 30.

Westesen et al teach nanoparticles containing various poorly water-soluble drugs. See abstract. Westesen teaches the use of an amorphous form of the drug to provide for better solubility and bioavailability of poorly water-soluble drugs than utilizing a crystalline form. See column 5, lines 45-56. Generally amorphous forms of a

substance exhibit a higher solubility and a faster dissolution than the crystals forms since they do not require lattice energy.

Kunz et al teach methods for inhibiting stenosis following vascular trauma or disease, cancer, diseases resulting from hyperactivity or hyperplasia of somatic cells. Example 7 discloses smooth muscle proliferation in the neointima. Kunz teaches direct or targeted delivery of therapeutic agents to vascular smooth muscle cells. See column 1, lines 15-35. Inhibiting stenosis following angioplasty is contemplated. See column 3, lines 54-62. The dosage forms are preferably in biodegradable microparticulates or nanoparticulates wherein the particles are formed of a polymer-containing matrix that biodegrades. Kunz et al teach conjugating the drug with a binding protein to target the cells and reduce toxicity. Example 7 notes the toxicity of a free drug versus a conjugated drug. See column 14, lines 25-33. Kunz teaches protein-coated particulates. See column 25, line 20 to column 26, line 40. Therapeutic agents such as taxol or analogs are preferred therapeutic agents that are designed to target the cell activity without killing the cell. Taxol is taken into the cell and stabilizes the cell from further dividing. See column 4, lines 40-45 and column 13, lines 24-27. Examples of dosages include .001 to 100 mg/kg per day. See column 28, line 48. For prevention of restenosis following angioplasty or an intervention that contributes to the acute proliferation of smooth muscle cells, a single pre-loading dose is given prior to or at the time of intervention with smaller chronic doses given two or three weeks after intervention. For example, a single dose may be administered about 24 hours prior to intervention, while

multiple preloading doses may be administered daily for several days prior to intervention. See column 29, lines 10-15. Delivery of the active agents may be intravenous, intra-arterial (stents), or local delivery. See column 30, lines 56-65 and examples for stent deployment. Kunz teaches single administration protocol. See column 36, lines 50-55. Example 6 teaches infusion using a balloon catheter. Administration to a carotid, femoral, and coronary artery is taught. See examples. Example 3 teaches administering the dose in less than three to five minutes. Also note example 5 and 14.

Firstly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to look to the guidance provided by Hunter and utilize albumin as the polymer of choice. One would have been motivated to do so with a reasonable expectation of success and similar results since Hunter suggests proteins and polypeptides such as albumin are suitable as the polymeric carrier. Alternatively, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Hunter and Yapel and specifically utilize albumin as the polymeric carrier. One would have been motivated to do so since Yapel teaches the advantages of using albumin as the polymeric carrier including nonantigenicity, localized and targeted delivery which reduces toxicity of anti-neoplastic drugs, ease of preparation, etc.

Secondly, although it is the examiner's position that Hunter implicitly teaches the instant delivery time, i.e. by inserting a stent, it would have been obvious to administer the product in less than 30 minutes. One would have been motivated to

do so since Kunz teaches administering microparticles and nanoparticles containing an antineoplastic drug via injections and stents in a single does regimen under 30 minutes. Further, Kunz teaches the dosing cycles to treat restenosis. A skilled artisan would have reasonably expected success and similar results since both Hunter and Kunz teach the treatment of recurrent stenosis and neointimal hyperplasia with drugs that inhibit microtubule function such as taxol. Therefore, it would have been obvious to look to Kunz to determine the appropriate delivery and dosing times to treat the same disease using the same delivery vehicle and drug.

Lastly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize an amorphous drug form. One would have been motivated to do so since Westesen teaches the use of an amorphous form for better solubility and bioavailability of poorly water-soluble drugs.

Response to Arguments

Applicant's arguments filed 10/14/09 have been fully considered but they are not persuasive. Applicant arguments regarding Kunz and Westesen have been addressed above. Applicants argue that Hunter does not cure the deficiencies of Desai and Westesen because Hunter does not teach or suggest that systemically administering a therapeutic agent in nanoparticle form, coated in a coating consisting essentially of protein, in 30 minutes or less, would be effective in treating hyperplasia of non-cancerous cells in a blood vessel. The argument is not persuasive because Hunter is taught for the use of paclitaxel in treating hyperplasia and the teaching of a nanoparticle of protein shell comprising the drug comes from Desai.

Applicant argues that Hunter teaches a stent and the instant recitation, "wherein the effective amount of the composition is systemically administered in less than 30 minutes," clearly does not encompass deployment of a stent. It is argued that the delivery by stent is distinct from systemic delivery, as emphasized in the instant application. The arguments are not persuasive because Hunter is not limited to using stents. Hunter teaches administration intrarticularly, intraocularly, intranasally, intradermal, sublingually, orally, topically, intravesically, intrathecally, topically, intravenously, intraperitoneally, intracranially, intramuscularly, and subcutaneously to the disease site. See column 38, lines 1-10. Applicants' arguments that Hunter generally teaches the above routes is not persuasive because Hunter describes the various routes of administration and choosing an appropriate route so as to achieve the desired release of a drug would have been within the scope of a skilled artisan.

Applicant argues that Kunz does not teach a method of administering an effective amount of a composition comprising an amorphous drug in nanoparticle form, coated with a coating consisting essentially of protein, wherein the effective amount of the composition is systemically administered in less than about 30 minutes. Furthermore, as discussed above, Kunz teaches away from such a method.

Kunz has been discussed above and incorporated herein.

Applicant argues that Yapel does not teach a method of treating non-cancerous cell proliferation in blood vessels, or systemically administering an effective amount of a nanoparticle drug composition in less than about 30 minutes for such purpose.

As discussed above, Hunter teaches the instant method of treating non-cancerous hyperplasia in the instant time frame. It is the examiner's position that Hunter implicitly teaches the delivery time. It is noted that Hunter teaches inserting a coated stent. Thus, although Hunter does not explicitly state that this is done under 30 minutes, the examiner points out that this is implicit since it takes less than 30 minute to place the catheter into a site. Further, Hunter suggests the use of protein particles such as albumin. Yapel is only relied upon to provide further motivation to utilize albumin. Therefore, applicant's argument is unpersuasive.

Claims 36-37, 44-45, 52-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hunter et al (5,716,981) by itself or in view of Yapel (4,147,767) in view of Kunz et al (5,733,925) and Westesen et al (6,197,349) in further in view of Marx (Circ. Res. Vol. 76, pp. 412-417, 1995).

The disclosure of Hunter, Yapel, Kunz, and Westesen have been set forth above.

The references do not teach the specific use of rapamycin as the antiproliferative agent.

Marx teaches rapamycin is an inhibitor of smooth muscle cells in the abnormal proliferation of restenosis. See abstract.

It would have been obvious for one of ordinary skill in the art at the time the invention was made to combine the teaching of the above references and utilize the instantly claimed drugs. One would have been motivated to do so with a

reasonable expectation of success since Marx teaches the rapamycin is a smooth cell inhibitor useful in treating restenosis. The selection of a specific drug is considered prima facie obvious to a skilled artisan in the art.

Response to Arguments

Applicant's arguments filed 10/14/09 have been fully considered but they are not persuasive.

Applicant argues the merits of Hunter, Yapel, Kunz, and Westesen, which have been addressed above and incorporated herein. It is argued that Marx does not cure the deficiencies of other references. Since applicant has not addressed the instant rejection specifically, the rejection is maintained for the reasons set forth in the rejection.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir.

1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3-5, 7-14, 17, 31-33, 38-41, 46-49, 54-55, 57-96 over claims 1-2, 5-18 11/594417; and instant claims 1, 3-14, 17, 31-33, 38-41, 46-49, 54-55, 57-96 over claims 1-7, 11-20, 44-45 of 11/359286 respectively in view of Hunter et al and Westesen.

The instant application is directed to a method of treating hyperplasia in the blood vessels and a method of reducing proliferation in vascular procedures comprising administering an antineoplastic; antiproliferative; or angiogenesis inhibitor coated with a protein.

Copending application '286 is directed to a method of treating a proliferative disease in an individual comprising administering to the individual: a) an effective amount of a composition comprising nanoparticles comprising a taxane and an albumin, and b)

an effective amount of at least one other chemotherapeutic agent, wherein said chemotherapeutic agent is selected from the group consisting of antimetabolites, platinum-based agents, alkylating agents, tyrosine kinase inhibitors, anthracycline antibiotics, vinca alkoids, proteasome inhibitors, macrolides, and topoisomerase inhibitors. Dependent claims are directed to rapamycin, albumin, the instant route of administration; and particle size.

Copending application '417 is directed to a method of treating a proliferative disease in an individual, comprising administering to the individual an effective amount of a composition comprising nanoparticles comprising a taxane and a carrier protein. Dependent claims are directed to albumin, the instant route of administration; and particle size.

The copending applications do not specify the proliferative disease.

Hunter et al teach anti-angiogenic compositions comprising an anti-angiogenic factor and a polymeric carrier and methods of its use. See abstract and column 3, lines 40-45. Preferably the active compound is a compound that disrupts microtubule function such as paclitaxel, epothilone, and etc. see column 3, lines 60-65. The polymeric carrier may be chosen from a carbohydrate, protein, or polypeptide such as albumin, collagen, and gelatin. See column 18, lines 15-30. Hunter teaches using the composition to coat a stent which is inserted into the body. Delivery may be done through via expandable catheters. See column 4, lines 24-30 and column 22. Hunter teaches the use of the composition to treat non-tumorigenic angiogenesis dependent diseases. See column 5, lines 44-46 and column 36, lines 9-15. Specifically Hunter

teaches methods of eliminating vascular obstructions in arteries and veins to prevent recurrent stenosis at the site of failed angioplasty and to treat post surgical narrowing. Suitable sites of the stent include iliac, renal, and femoral, and coronary arteries. See column 25, lines 48-67. Hunter teaches treating neointimal hyperplasia wherein a stent is coated with the composition and inserted onto the arteries. See column 36, lines 1-20. The composition may be further administered intracutaneously, intravenously, etc. see column 37, line 67 to column 38, lines 1-10. The microspheres range from 50-nm to 500 microns depending on the particular use. See column 17, lines 25-40. Anti-angiogenic factors may be linked by occlusion in the matrices of the polymer, bound by covalent linkages, or encapsulated in microcapsules. See column 17, lines 1-5. Hunter teaches administering the anti-angiogenic composition using a stent. Example 7 teaches inserting the stent into a rat. It should be noted that insertion of the stent would meet the instant delivery time since the composition is delivered to the site in less than 30 minutes (the time it takes to insert a stent is less than 30 minutes).

Westesen et al teach nanoparticles containing various poorly water-soluble drugs. See abstract. Westesen teaches the use of an amorphous form of the drug to provide for better solubility and bioavailability of poorly water-soluble drugs than utilizing a crystalline form. See column 5, lines 45-56. Generally amorphous forms of a substance exhibit a higher solubility and a faster dissolution than the crystals forms since they do not require lattice energy.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the copending applications and Hunter to arrive at the instantly claimed invention of treating hyperplasia of blood vessels and deliver the composition in less than 30 minutes. One would have been motivated to do so since Hunter teaches neointimal hyperplasia is a proliferative disease that can be treated with anti-neoplastic drugs that disrupt microtubule function. Therefore, although the copending application do not specify treating hyperplasia, instant application and copending applications are directed to similar subject matter since hyperplasia is a proliferative disease.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize an amorphous drug form. One would have been motivated to do so since Westesen teaches the use of an amorphous form for better solubility and bioavailability of poorly water-soluble drugs.

This is a provisional obviousness-type double patenting rejection.

Response to Arguments

Applicants request that the provisional rejections be held in abeyance until the office has made a determination of allowable subject matter. Since applicants did not argue the merits of the rejection and since there are no allowable claims, the rejection of record has been maintained.

Conclusion

This is a continuation of applicant's earlier Application No. 09/847945. All claims are drawn to the same invention claimed in the earlier application and could have been

finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lakshmi S. Channavajjala whose telephone number is 571-272-0591. The examiner can normally be reached on 9.00 AM -5.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila G. Landau can be reached on 571-272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lakshmi S Channavajjala/
Primary Examiner, Art Unit 1611
December 21, 2009